(2) computer program code for causing a computer to compare repeat sequence-free subsequences within said genomic region of interest to a nucleotide sequence database, whereby at least one repeat sequence-free subsequences that is at least 90% identical to a nucleotide sequence within said nucleotide sequence database is discarded;

(3) computer program code for causing a computer to identify oligonucleotide sequences that are suitable for use as primers in an amplification reaction to amplify a product within at least one repeat sequence-free subsequences remaining after executing said computer program code in element (2); and

(4) computer program code for outputting said oligonucleotide sequences.

REMARKS

I. Status of the Claims

Claims 1, 3, 9-10, 18, 20, 25-26, 34-35, and 37-38 are amended and claims 43-61 are added with this Amendment. Claim 8, 24, and 36 are canceled without prejudice to further prosecution. Therefore, claims 1-7, 9-23, 25-35, 37-38, and 40-59 are pending with entry of this Amendment. Claims 1-38 and 40-42 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Repeatmasker™ software in view of Redasoft™ as evidenced by Butler.

II. Support for the Amendments

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted. Claims 1, 18, 34 have been amended to recite "5 or fewer sequences that are at least 50% identical," and claims 9-10, 25-26, and 37-38 have been amended to recite "5 or fewer." Support for these amendments can be found in the specification, for example, on page 3, lines 19-24; page 11, lines 25-29; and page 12, lines 4-10. Claims 3, 20, and 35 have been amended to recite "repeat sequence-free subsequences that lacks any sequences that are at least 50% identical to said nucleotide

sequence database." Support for the amendment to claims 3, 20, and 35 can be found in the specification, for example, page 3, lines 19-24; page 4, lines 14-15 and page 12, lines 4-10 . Support for new claims 43-61 can be found in the specification, for example, on page 5, lines 15-22; page 6, lines 19-28; page 11, line 25 to page 12 line 4; and Figure 1. Therefore, no new matter is introduced with this amendment.

III. Rejection under 35 U.S.C. § 103(a)

Claims 1-38 and 40-42 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Repeatmasker™ software in view of Redasoft™ as evidenced by Butler. Specifically, the Examiner states that the RepeatMasker™ software discloses steps of identifying repeat sequences and comparing sequences in a database to generate potential primers and the Redasoft™ program teaches primer design. The Examiner alleges that the combination of Repeatmasker™ software and Redasoft™ meets all the limitations of claims 1-38 and 40-42. The Examiner further alleges that the motivation to combine Repeatmasker™ software and Redasoft™ is found in Butler, which was developed to combine various sequence analysis programs to analyze publicly available databases.

Applicants respectfully submit that the combination of Repeatmasker™ software in view of Redasoft™ as evidenced by Butler does not meet all the limitations of the currently pending claims. The Examiner appears to suggest that a method of selecting repeat sequence-free subsequences using Repeatmasker™ and performing a BLAST search to identify selected subsequences ***with homologs*** in a database for primer design is analogous to the presently claimed invention. However, the claims are, in fact, directed to a method of selecting repeat sequence-free subsequences and performing a search to identify subsequences with ***few and preferably no homologs*** in a database.

To clarify this distinction, Applicants have added independent claim 43, which recites "at least one repeat sequence-free subsequences that is at least 90% identical to a nucleotide sequence within said nucleotide sequence database is ***discarded***." In addition, Applicants have amended claims 1, 3, 9-10, 18, 20, 25-26, 34-35, and 37-38 to clarify that the claimed process involves selecting primers capable of amplifying a product within a subsequence for which "***5 or fewer*** sequences that are at least 50% identical are identified."

Applicants respectfully submit that none of the references cited teach or suggest ***discarding*** repeat sequence-free subsequences that are at least 90% identical to a nucleotide sequences in a database, as in independent claim 43. In addition, none of the cited references teach or suggest the identification of primers to amplify products within subsequences having at least 50% identity to ***5 or fewer*** sequences in a database, as in independent claims 1, 18, and 34.

A. None of the Cited References Teach or Suggest Identification of Primers to Amplify Products Within Subsequences Having 5 or Fewer Homologs in a Database

Independent claims 1, 18, and 34, as currently amended, are drawn to the identification or selection of oligonucleotide sequences for use as primers to amplify a product within repeat sequence-free subsequences. As amended, at least one of the repeat sequence-free subsequences must have a limited number (i.e. 5 or fewer) of homologous sequences (i.e. at least 50% identity in claims 1, 18, and 34) in a database. Specifically, lines 11-15 of claim 1 recites:

> executing a third process on a digital computer to identify oligonucleotide sequences that are suitable for use as primers in an amplification reaction to amplify a product within at least one of said repeat sequence-free subsequences for which 5 or fewer sequences that are at least 50% identical are identified in said nucleotide sequence database.

None of the cited references disclose a software program containing a limit on the number of homologous sequences in a repeat sequence-free subsequence used for primer selection.

The Examiner states that "Applicant claims that the Repeatmasker™ software does not teach or suggest using this software in combination with BLAST™." On the contrary, Applicants agree with the Examiner's assertion that the Repeatmasker™ documentation teaches the use of Repeatmasker™ software in combination with BLAST. However, Applicants assert that the Repeatmasker™ documentation fails to provide any motivation to use BLAST to identify primers for amplification of products within subsequences having limited or no homologs in a database. Furthermore, Applicants assert

that the Repeatmasker™ documentation teaches away from limiting the number of homologous sequences in a repeat sequence-free subsequence.

For example, the RepeatMasker documentation directed to the use of BLAST searches cautions that "[t]he most common concern is of course if RepeatMasker ever masks coding regions." *See*, last paragraph of page 5 of RepeatMasker documentation. The reason that masking of coding regions for BLAST searches is a common concern is because BLAST is commonly used in the art to identify the ***highest possible number*** of homologous coding sequences in a database. By masking the coding region of repeat sequence-free subsequences, fewer homologous coding sequences are identified. By contrast, Applicants' invention seeks to identify a repeat sequence-free subsequence with ***5 or fewer*** homologous sequences (e.g. at least 50% identical). Therefore, the RepeatMasker documentation teaches away from Applicants claimed invention reciting "5 or fewer sequences that are at least 50% identical."

Moreover, claims 3, 20, and 35 are directed to embodiments where primers are designed to amplify repeat free-sequence subsequences that ***lack any*** sequences at least 50% identical to sequences in the database. The Examiner has not cited any reference that teaches or suggests identification of primers that amplify subsequences that are not related to sequences in the database. Accordingly, Applicants submit that claims 3, 20 and 35 are non-obvious over the prior art.

B. None of the Cited References Teach or Suggest Discarding Repeat Sequence-Free Subsequences

New claim 43 is drawn to a method comprising ***discarding*** at least one repeat sequence-free subsequences having at least 90% identity to a nucleotide sequence in a database. None of the cited references disclose a software program that ***discards*** repeat sequence-free subsequences. In fact, the cited references teach away from Applicants' invention by describing the desirability of repeat sequence-free subsequences that are homologous to nucleotide sequences in a database rather than discarding such subsequences. *See, e.g.*, the discussion above regarding the RepeatMasker documentation directed to the use of BLAST searches. Therefore, the cited art teaches away from Applicants claimed

invention reciting "whereby all repeat sequence-free subsequences that are at least 90% identical to a nucleotide sequence within said nucleotide sequence database are discarded."

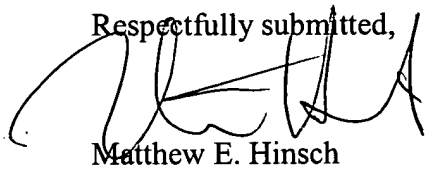
C. Summary

None of the cited references teach or suggest methods comprising identifying primer sequences that amplify products within a repeat sequence-free subsequence where that subsequence has 5 or less sequences in a database that are at least 50% identical. In addition, none of the cited references disclose discarding a repeat sequence-free subsequence that is at least 90% identical to a nucleotide sequence in a database. Indeed, if anything, the RepeatMasker™ documentation teaches away from Applicants' invention as claimed. Therefore, the combination of Repeatmasker™ software in view of Redasoft™ as evidenced by Butler does render obvious Applicants claimed invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. Should any matters remain that can be resolved by a personal conference, the Examiner is encouraged to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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